WEST Search History

DATE: Tuesday, July 15, 2003

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB; THES=ASSIGNEE; PLUR=YES; OP=ADJ			
L1	(arsen$).clm. and (prodrug$1 or pro drug$1).clm.	0	L1

END OF SEARCH HISTORY

```
FILE 'CAPLUS' ENTERED AT 17:22:27 ON 15 JUL 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'MEDLINE' ENTERED AT 17:22:27 ON 15 JUL 2003

FILE 'EMBASE' ENTERED AT 17:22:27 ON 15 JUL 2003
COPYRIGHT (C) 2003 Elsevier Science B.V.  All rights reserved.

FILE 'CANCERLIT' ENTERED AT 17:22:27 ON 15 JUL 2003

FILE 'USPATFULL' ENTERED AT 17:22:27 ON 15 JUL 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'PCTFULL' ENTERED AT 17:22:27 ON 15 JUL 2003
COPYRIGHT (C) 2003 Univentio

=> s arsen? (50a) (pro drug# or prodrug#)
   3 FILES SEARCHED...
L1          12 ARSEN? (50A) (PRO DRUG# OR PRODRUG#)

=> dup rem l1
PROCESSING COMPLETED FOR L1
L2          12 DUP REM L1 (0 DUPLICATES REMOVED)

=> d 1-12 bib hit

L2   ANSWER 1 OF 12  CAPLUS  COPYRIGHT 2003 ACS
AN   2003:376654  CAPLUS
DN   138:390922
TI   Arsenide compound system for selective targeting of apoptotic cells
IN   Hogg, Philip John
PA   Unisearch Limited, Australia
SO   PCT Int. Appl., 85 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
PI   WO 2003039564      A1   20030515       WO 2002-AU1523   20021108
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT,
             TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ,
             MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
             CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
             NE, SN, TD, TG
PRAI AU 2001-8746       A    20011108
OS   MARPAT 138:390922
RE.CNT  5     THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT   Drug delivery systems
        (prodrugs; arsenide compd. system for selective
        targeting of apoptotic cell)

L2   ANSWER 2 OF 12  USPATFULL
AN     2002:323216  USPATFULL
```

TI Compositions and methods for the treatment of primary and metastatic neoplastic diseases using arsenic compounds
IN Ellison, Ralph M., Palm Beach, FL, UNITED STATES
Mermelstein, Fred H., Clifton, NJ, UNITED STATES
PI US 2002183385 A1 20021205
AI US 1998-173531 A1 19981015 (9)
PRAI US 1997-62375P 19971015 (60)
DT Utility
FS APPLICATION
LREP STEPHEN A. BENT, FOLEY & LARDNER, 3000 K STREET, N.W., SUITE 500, WASHINGTON HARBOUR, WASHINGTON, DC, 20007-5109
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 4 Drawing Page(s)
LN.CNT 1343
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD [0043] The arsenic compound of the invention may be utilized in in a variety of known forms; for example, arsenic can be administered as a salt, an organic or inorganic complex, an organic chelate, an organic compound or an organic or inorganic solution. It is preferred that the form be chosen to reduce toxicity and improve efficacy. Further, the form chosen may also depend on the type and location of the tumor in question. The inorganic salt forms of arsenic are preferred. For example, inorganic salts such as arsenic triiodide, arsenic(III)bromide, arsenic(III)chloride, arsenic pentoxide, arsenic trioxide, Fowler's solution (potassium arsenite), sodium arsenite, and calcium arsenite may be used. Arsenic trioxide is most preferred. Both arsenous acids and arsenites as well as **arsenic** acids and **arsenates** may be used within the present methods. Aqueous solutions containing **arsenite** ions are preferred. Further, **arsenic** sulfides may be used such as **arsenous** sulfide, **arsenic** sulfide, **arsenic** pentasulfide, tetraarsenic trisulfide and tetraarsenic pentasulfide. Without being limited by any theory, certain of these **arsenic** compounds may be **prodrugs** to an active species.
DETD [0046] As used herein, "**arsenic** compound" refers to a pharmaceutically acceptable form of **arsenic** including salts, solutions, complexes, chelates and organic and inorganic compounds incorporating **arsenic**. It should be recognized that the invention includes **arsenic prodrugs** or compounds that are converted in vivo to biologically active forms of **arsenic**. Such **prodrugs** may be used to reduce or avoid the well known potential for **arsenic** toxicity. The **arsenic** compounds of the present invention can be synthesized or commercially purchased. For example, the compounds can be prepared from well-known chemical techniques. (See for example, Kirk-Othmer, Encyclopedia of Chemical Technology 4 ed. volume 3 pps. 633-655 John Wiley & Sons).

L2 ANSWER 3 OF 12 USPATFULL
AN 2002:157658 USPATFULL
TI Retinoid compounds (I)
IN Lapierre, Jean-Marc, Mountain View, CA, UNITED STATES
Rotstein, David Mark, Sunnyvale, CA, UNITED STATES
Sjogren, Eric Brian, Mountain View, CA, UNITED STATES
PI US 2002082265 A1 20020627
AI US 2001-968425 A1 20011001 (9)
PRAI US 2000-237459P 20001002 (60)
DT Utility
FS APPLICATION
LREP ROCHE BIOSCIENCE, 3401 HILLVIEW AVENUE, INTELLECTUAL PROPERTY LAW DEPT., MS A2-250, PALO ALTO, CA, 94304-9819
CLMN Number of Claims: 100
ECL Exemplary Claim: 1

DRWN No Drawings
LN.CNT 4224
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0225] In a still another aspect, the current invention provides a method for preventing cancer in a human at risk of cancer (e.g., smokers, asbestos workers and uranium workers) by administering a amount of a compound of the invention or **pro-drug** thereof, sufficient to prevent cancer. Examples of premalignant and precancerous lesions or tumors which may be prevented by compounds of the invention include, but are not limited to, actinic and **arsenic** keratoses, dysplasias and papillomas of mucous membranes and precancerous changes of the bladder.

L2 ANSWER 4 OF 12 PCTFULL COPYRIGHT 2003 Univentio
AN 2002028810 PCTFULL ED 20020627 EW 200215
TIEN NEW RETINOIDS FOR THE TREATMENT OF EMPHYSEMA
TIFR NOUVEAUX RETINOIDES DESTINES AU TRAITEMENT DE L'EMPHYSEME
IN LAPIERRE, Jean-Marc, 1240 Dale Av.#19, Mountain View, CA 94040, US; ROTSTEIN, David, Mark, 939 Lorne Way, Sunnyvale, CA 94087, US; SJOGREN, Eric, Brian, 442 Dell Avenue, Mountain View, CA 94043, US
PA F. HOFFMANN-LA ROCHE AG, 124 Grenzacharstrasse, CH-4070 Basle, CH [CH, CH]
AG KJELLSAA-BERGER, Hanny, 124 Grenzacherstrasse, CH-4070 Basle, CH
LAF English
LA English
DT Patent
PI WO 2002028810 A2 20020411
DS W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZW
RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
AI WO 2001-EP11017 A 20010924
PRAI US 2000-60/237,459 20001002

DETD In a still another aspect, the current invention provides a method for preventing cancer in a human at risk of cancer (e.g., smokers, asbestos workers and uranium workers) by adn-dnistering a amount of a compound of the invention or **pro-drug** thereof, sufficient to prevent cancer. Examples of premalignant and precancerous lesions or tumors which may be prevented by compounds of the invention include, but are not limited to, actinic and **arsenic** keratoses, dysplasias and papillomas of mucous membranes and precancerous changes of the bladder
Another aspect of the present invention provides a pharmaceutical composition that prevents cancer in a human at risk of cancer. The composition comprises an amount of a compound of the invention or **pro-drug** thereof, and a pharmaceutically acceptable carrier that is sufficient to prevent cancer.

L2 ANSWER 5 OF 12 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2002384998 EMBASE

TI New drugs for the treatment of chronic lymphocytic leukemia.
AU Cheson B.D.; Dancey J.; Murgo A.
CS Dr. B.D. Cheson, National Cancer Institute, Executive Plaza North, Bethesda, MD 20892, United States. chesonb@ctep.nci.nih.gov
SO Reviews in Clinical and Experimental Hematology, (2000) 4/2 (145-166). Refs: 141
ISSN: 1127-0020 CODEN: RCEHFB
CY United Kingdom
DT Journal; General Review
FS 016 Cancer
025 Hematology
037 Drug Literature Index
LA English
SL English
AB Novel strategies are needed to improve the prognosis of patients with chronic lymphocytic leukemia (CLL). One approach is to identify new drugs with unique mechanisms of action. Compound GW506U78, the **prodrug** for arabinosylguanine, is an interesting new purine analog, which induces responses in about one-third of patients with relapsed or refractory CLL. A multicenter study is currently evaluating patients with CLL who have failed treatment with both fludarabine and an alkylating agent. Other agents in clinical development include retinoids and **arsenicals** which induce apoptosis, farnesyl transferase inhibitors, proteasome inhibitors and the signal transduction modulators, bryostatin and UCN-01. UCN-01 not only inhibits protein kinase C, but also modulates the G(2) checkpoint. In vitro synergy has been demonstrated with fludarabine and a phase I trial of this combination is ongoing at the National Cancer Institute, USA. Flavopiridol is a semisynthetic flavone derivative which is active against cycling as well as noncycling cells. It inhibits a variety of cyclins and induces apoptosis. The histone deacetylase inhibitor depsipeptide has selective activity against CLL cells in vitro. An increasing body of evidence has implicated angiogenesis in hematologic malignancies, such as multiple myeloma, lymphoma and CLL. Several angiogenesis inhibitors are currently in clinical trials, including thalidomide, SU5416 and SU6668. Future strategies must be directed at appropriate therapeutic targets using rational combinations of these drugs and other new compounds with the goal of curing patients with CLL.

L2 ANSWER 6 OF 12 PCTFULL COPYRIGHT 2003 Univentio
AN 1999018798 PCTFULL ED 20020515
TIEN COMPOSITIONS AND METHODS FOR THE TREATMENT OF PRIMARY AND METASTATIC NEOPLASTIC DISEASES USING ARSENIC COMPOUNDS
TIFR COMPOSITIONS ET METHODES DE TRAITEMENT DE MALADIES NEOPLASIQUES PRIMITIVES ET METASTATIQUES A L'AIDE DE COMPOSES D'ARSENIC
IN ELLISON, Ralph, M.;
MERMELSTEIN, Fred, H.
PA POLARX BIOPHARMACEUTICALS, INC.
LA English
DT Patent
PI WO 9918798 A1 19990422
DS W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
AI WO 1998-US21782 A 19981015
PRAI US 1997-60/062,375 19971015

DETD The invention includes a method for treating disorders of blood in mammal which comprises administering one or more arsenic compound in a therapeutically effective and non-lethal amount,

The arsenic compound of the invention may be utilized in in a variety of known forms; for example, arsenic can be administered as a salt, an organic or inorganic complex, an organic chelate, an organic compound or an organic or inorganic solution. It is preferred that the form be chosen to reduce toxicity and improve efficacy, Further, the form chosen may also depend on the type and location of the tumor in question. The inorganic salt forms of arsenic are preferred, For example, inorganic salts such as arsenic triiodide, arsenic(III)bromide, arsenic(III)chloride, arsenic pentoxide, arsenic trioxide, Fowler's solution (potassium arsenite), sodium arsenite, and calcium arsenite may be used, Arsenic trioxide is most preferred. Both arsenous acids and arsenites as well as **arsenic** acids and **arsenates** may be used within the present methods. Aqueous solutions containing **arsenite** ions are preferred. Further, **arsenic** sulfides may be used such as **arsenous** sulfide, **arsenic** sulfide, **arsenic** pentasulfide, tetraarsenic trisulfide and tetraarsenic pentasulfide. Without being limited by any theory, certain of these **arsenic** compounds may be **prodrugs** to an active species.

Arsenic can also be readily combined with carbon to form a wide variety of organic compounds, These include but are not limited to primary and secondary arsines, tertiary arsines, halo arsines, dihalo arsines, cyclic and polymeric substances containing arsenic; specific examples of organic arsenic compounds include but are not limited to 3-Nitro hydroxyphenylarsonic acid, arsanilic acid, sodium hydrogen 4-aminophenylarsenate, melarsoprol, melarsonyl potassium, carbarsone, **arsenamide** arsphenamine and sodium arsanilate, As used herein,, **arsenic** compound refers to a pharmaceutically acceptable form of **arsenic** including salts, solutions, complexes, chelates and organic and inorganic compounds incorporating **arsenic**. It should be recognized that the invention includes **arsenic prodrugs** or compounds that are converted in vivo to biologically active forms of **arsenic**. Such **prodrugs** may be used to reduce or avoid the well known potential for **arsenic** toxicity. The **arsenic** compounds of the present invention can be synthesized or commercially purchased. For example, the compounds can be prepared from well-known chemical techniques. (See for example, Kirk-Othmer, Encyclopedia of Chemical Technology 4 ed. volume 3 pps, 633-655 John Wiley & Sons), In one embodiment, the arsenic compound of the invention is arsenic trioxide which is dissolved in an aqueous solution of sodium hydroxide, with the pH adjusted to a physiologically acceptable range, e.g. about pH 6 Any suitable mode of administration may be used in accordance with the present invention including but not limited to parenteral administration such as intravenous, subcutaneous, intramuscular and intrathecal administration; oral, intranasal, rectal or vaginal administration may also be used; directly into the tumor; transdermal patches; implant devices (particularly for slow release); finally, topical administration may be used. The mode of administration will vary according to the type of arsenic

compound being used and the disease to be treated, The pharmaceutical compositions to be used may be in the form of sterile physiologically acceptable (aqueous or organic) solutions, colloidal suspensions, creams, ointments, pastes, capsules, caplets, tablets and cachets. The pharmaceutical compositions comprising arsenic compounds of the invention can be contained in sealed sterile glass containers and/or ampoules, Further, the active ingredient may be micro-encapsulated, encapsulated in a liposome, noisome or lipofoam alone or in conjunction with targeting antibodies. It should be recognized that delayed slow or sustained release forms of administration are also included.

L2 ANSWER 7 OF 12 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 1999222426 EMBASE
TI Mechanisms of pyrazinamide resistance in mycobacteria: Importance of lack of uptake in addition to lack of pyrazinamidase activity.
AU Raynaud C.; Laneelle M.-A.; Senaratne R.H.; Draper P.; Laneelle G.; Daffe M.
CS M. Daffe, Inst. Pharmacologie Biologie Struct., CNRS, Universite Paul Sabatier, 205 route de Narbonne, 31077 Toulouse cedex, France. daffe@ipbs.fr
SO Microbiology, (1999) 145/6 (1359-1367).
Refs: 39
ISSN: 1350-0872 CODEN: MROBEO
CY United Kingdom
DT Journal; Article
FS 004 Microbiology
037 Drug Literature Index
LA English
SL English
AB Mycobacteria are known to acquire resistance to the antituberculous drug pyrazinamide (PZA) through mutations in the gene encoding pyrazinamidase (PZase), an enzyme that converts PZA into pyrazinoic acid, the presumed active form of PZA against bacteria. Additional mechanisms of resistance to the drug are known to exist but have not been fully investigated. Among these is the non-uptake of the pro-drug, a possibility investigated in the present study. The uptake mechanism of PZA, a requisite step for the activation of the **pro-drug**, was studied in Mycobacterium tuberculosis. The incorporation of [14C]PZA by the bacilli was followed in both neutral and acidic environments since PZA activity is known to be optimal at acidic pH. By using a protonophore (carbonyl cyanide m-chlorophenylhydrazone; CCCP), valinomycin, **arsenate** and low temperature, it was shown that an ATP-dependent transport system is involved in the uptake of PZA. Whilst the structurally analogous compound nicotinamide inhibited the transport system of PZA, other structurally related compounds such as pyrazinoic acid, isoniazid and cytosine did not. Acidic conditions were also without effect. Based on diffusion experiments in liposomes, it was found that PZA diffuses rapidly through membrane bilayers, faster than glycerol, whilst the presence of OmpATb, the porin-like protein of M. tuberculosis, in proteoliposomes slightly increased the diffusion of the drug. This finding may explain why the cell wall mycolate hydrophobic layer does not represent the limiting step in the diffusion of PZA, as judged from comparative experiments using a M. tuberculosis strain and its isogenic mutant elaborating 40% less covalently linked mycolates. PZase activity, and PZA uptake and susceptibility in different mycobacterial species were compared. M. tuberculosis, a naturally PZA-susceptible species, was the only species that exhibited both PZase activity and PZA uptake; no such correlation was observed with the four naturally resistant species examined. Mycobacterium smegmatis possessed a functional PZase but did not take up PZA; the reverse was true for the PZase-negative strain of Mycobacterium avium used, with PZA uptake comparable to that of M. tuberculosis. Mycobacterium

bovis BCG and Mycobacterium kansasii exhibited neither a PZase activity nor PZA uptake. These data clearly demonstrate that one of the mechanisms of resistance to PZA resides in the failure of strains to take up the drug, indicating that susceptibility to PZA in mycobacteria requires both the presence of a functional PZase and a PZA transport system. No correlation was observed between the occurrence and cellular location of PZase and of nicotinamidase in the strains examined, suggesting that one or both amides can be hydrolysed by other mycobacterial amidases.

L2 ANSWER 8 OF 12 USPATFULL
AN 1998:131412 USPATFULL
TI Method for loading lipsomes with ionizable phosphorylated hydrophobic compounds, pharmaceutical preparations and a method for administering the preparations
IN Mehlhorn, Rolf Joachim, Richmond, CA, United States
PA The Reagents of the University of California, Oakland, CA, United States (U.S. corporation)
PI US 5827532 19981027
AI US 1997-791557 19970131 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Kishore, Gollamudi S.
LREP Burns, Doane, Swecker & Mathis, L.L.P.
CLMN Number of Claims: 18
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 864
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM Multidrug anticancer therapies appear to offer great promise. The effectiveness of multidrug treatment of HIV may be seen again in treating neoplasms. However, as many effective anticancer drugs are not directly amenable to remote loading (i.e., loading with pH gradients), either because they are too highly charged (methotrexate) or lack pH responsive groups (taxol) there is a need for chemically modifying available cancer agents to allow their use in liposome remote loading. Chemical modification, e.g., to create **pro-drugs** or inherently superior drugs, thus considerably broadens the **arsenal** of liposomal anticancer therapies. Of course, chemical modification also has the potential to enhance therapeutic effectiveness, e.g., of extremely hydrophobic drugs that partition into fatty tissues rather than target organs.

L2 ANSWER 9 OF 12 PCTFULL COPYRIGHT 2003 Univentio
AN 1998033484 PCTFULL ED 20020514
TIEN A METHOD FOR LOADING LIPOSOMES WITH IONIZABLE PHOSPHORYLATED HYDROPHOBIC COMPOUNDS
TIFR METHODE POUR PIEGER DES COMPOSES HYDROPHOBES PHOSPHORYLES IONISABLES DANS DES LIPOSOMES
IN MEHLHORN, Rolf, J.
PA THE REGENTS OF THE UNIVERSITY OF CALIFORNIA
LA English
DT Patent
PI WO 9833484 A1 19980806
DS W: CA JP AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
AI WO 1998-US1469 A 19980127
PRAI US 1997-8/791,557 19970131

DETD PCT/US85/01501, published February 27, 1986 (International Publication No. WO 98/33484 PCT/US98/01469
a need for chemically modifying available cancer agents to allow their use in
liposome remote loading. Chemical modification, e.g., to create **pro-drugs** or

inherently superior drugs, thus considerably broadens the **arsenal** of liposornal
anticancer therapies. Of course, chemical modification also has the potential to
enhance therapeutic effectiveness, e.g., of extremely hydrophobic drugs that
partition into fatty tissues rather than target organs.

L2 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2003 ACS
AN 1994:569431 CAPLUS
DN 121:169431
TI Design of Antitumor Prodrugs: Substrates for Antibody Targeted Enzymes
AU Jungheim, Louis N.; Shepherd, Timothy A.
CS Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA
SO Chemical Reviews (Washington, DC, United States) (1994), 94(6), 1553-66
CODEN: CHREAY; ISSN: 0009-2665
DT Journal; General Review
LA English
AB A review with 50 refs. discussing antibody-directed catalysis systems which are able to mediate antigen-mediated cytotoxicity both in vitro and in vivo. A wide variety of enzymes have been employed and a significant no. of prodrugs, which perform as designed, have been prepd. Exciting antitumor activity has been obsd. in vivo in at least 3 instances, using carboxypeptidases G2, alk. phosphatase, and .beta.-lactamase. Considering the **arsenal** of **prodrugs** described herein it seems that the continued development of the ADC concept will be more dependent upon the successful prodn. of highly selective and nonimmunogenic monoclonal antibody-enzyme conjugates than on the limitations of synthetic chem.

L2 ANSWER 11 OF 12 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 93291463 EMBASE
DN 1993291463
TI Therapeutic efficacy of new dimercaptosuccinic acid (DMSA) analogues in acute arsenic trioxide poisoning in mice.
AU Kreppel H.; Paepcke U.; Thiermann H.; Szinicz L.; Reichl F.X.; Singh P.K.; Jones M.M.
CS Institut Pharmakologie/Toxikologie, Akademie Sanitats-/Gesundheitswesens, Bundeswehr, BSW, Ingolstadter Landstrasse 100,D-85748 Garching, Germany
SO Archives of Toxicology, (1993) 67/8 (580-585).
ISSN: 0340-5761 CODEN: ARTODN
CY Germany
DT Journal; Article
FS 052 Toxicology
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB The therapeutic efficacy of six newly synthesized analogues of dimercaptosuccinic acid (DMSA) was investigated in acute **arsenic** trioxide poining in mice. Meso-2,3-di(acetylthio)succinic acid (DATSA) and meso-2,3-di(benzoylthio)succinic acid (DBTSA) are analogues of DMSA with protected thiol groups ('**prodrugs**'), and DMDMS, DEDMS, DnPDMS, and DiPDMS are various di-esters of DMSA with methyl, ethyl, n-propyl, and iso-propyl alcohols, respectively. Thirty minutes after s.c. injection of an LD80 of **arsenic** trioxide (65 .mu.mol/kg) male NMRI mice were treated with a single equimolar dose (0.7 mmol/kg) of DMSA i.p. or one of the analogues i.p. or via gastric tube (i.g.). Control animals received arsenic trioxide and saline 30 min later. The survival rate was recorded for 30 days. All of the animals treated with DMSA i.p. survived and all controls died within 2 days. Administered i.g., DATSA and DBTSA increased the survival rate to 29% and 43%, and injected i.p. to 86%. Treatment with DMDMS i.p. and i.g., and with DEDMS, DnPDMS, and DiPDMS i.g. did not reduce lethality. Given i.p., DnPDMS to 86%, respectively. To investigate

the efficacy of the DMSA analogues in reducing the tissue content of arsenic, male NMRI mice received an s.c. injection of an LD5 of arsenic trioxide containing a tracer dose of 73-As(III) (42.5 .mu.mol/kg body wt). Thirty minutes later, saline (controls) or a single equimolar dose (0.7 mmol/kg) of DMSA i.p., or one of the analogues i.p. or i.g. was administered. The arsenic content of various organs (blood, liver, kidneys, heart, lungs, spleen, small intestine, large intestine, brain, testes, skeletal muscle, and skin) at 30 min, 2 h, 4 h, 6 h, and 8 h after the arsenic injection was measured using a gamma counter. In all organs investigated, the efficacy of DATSA, DBTSA, DEDMS, and DnPDMS administered i.p and i.g., and of DiPDMS given i.p. in reducing the tissue content of arsenic was significantly higher compared to saline ($p < 0.05$), but superior to DMSA. Treatment with DMDMS i.p. or i.g., and DiPDMS i.g. showed much less or no reduction. Generally, the elimination rate of arsenic following therapy i.p. was more effective compared to i.g. treatment. Generally, the elimination rate of arsenic following therapy i.p. was more effective compared to i.g. treatment. It is concluded that DATSA and DBTSA, i.p. and i.g., and DEDMS, DnPDMS, and DiPDMS, given i.p., are effective arsenic antidotes, but are not superior to DMSA. Different substitution of the DMSA molecule resulted in altered therapeutic efficacy. The dependence of the antidotal efficacy on the route of administration (i.p., i.g.) indicates differences in absorption or metabolism of the analogues. Shielding of the thiol groups did not exhibit any advantage, high lipophilicity of an arsenic antidote might be unfavourable, and the limitation to the extracellular space might be the key to higher antidotal success in acute arsenic trioxide poisoning.

L2 ANSWER 12 OF 12 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 90139892 EMBASE
DN 1990139892
TI Meso-2,3-dimercaptosuccinic acid: Chemical, pharmacological and toxicological properties of an orally effective metal chelating agent.
AU Aposhian H.V.; Aposhian M.M.
CS Department of Molecular and Cellular Biology, University of Arizona, Tucson, AZ 85721, United States
SO Annual Review of Pharmacology and Toxicology, (1990) 30/- (279-306). ISSN: 0066-4251 CODEN: ARPTDI
CY United States
DT Journal; General Review
FS 023 Nuclear Medicine
029 Clinical Biochemistry
035 Occupational Health and Industrial Medicine
046 Environmental Health and Pollution Control
052 Toxicology
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB The primary purpose of this article is to summarize the recent investigations dealing with the pharmacology and toxicology of meso-2,3-dimercaptosuccinic acid, an orally effective chelating agent. The need for a better chelating agent for treating young children and pregnant women with lead intoxication has been apparent for some time. Preclinical and clinical evidence now indicate that meso-2,3-dimercaptosuccinic acid, an Orphan Drug, shows the most promise for being effective in this regard. It has an extracellular distribution that may be responsible for its low toxicity compared to other dithiols. No attempt has been made to compare it in a rigourous and thorough manner with other chelating agents. That has not been the purpose of this review. The advantages of meso-DMSA, however, compared to CaNa2EDTA for the treatment of lead intoxication, have been outlined. Significant advances have been made recently in elucidating the structures of the metal chelates of DMSA. There is a striking difference between the structures of the lead chelate of meso-DMSA and those of racemic-DMSA. The former chelates by coordination

of one sulfur and one oxygen atom with Pb. The letter can form chelates via the two sulphur atoms or via one oxygen and one sulfur atom. Solubility of the lead chelates depends on the ionization of the noncoordinated thiol and carboxylic acid groups. Bimane derivatization, HPLC, and fluorescence, as well as gas chromatography can be used for analysis of DNSA in biological fluids. The acid dissociation constants for meso- and recemic-DMSA have been summarized from the literature as have the formation constants of some of the DMSA chelates. DMSA is biotransformed to a mixed disulfide in humans. By 14 hr after DMSA administration (10 mg/kg), only 2.5% of the administered DMSA is excreted in the urine as unaltered DMSA and 18.1% or the dose is found in the urine as altered forms of DMSA. Most altered DMSA in the urine is in the form of a mixed dislfide. It consists of DMSA in disulfide linkages with two molecules of L-cysteine. One molecule of cysteine is attached to each of the sulfur atoms of DMSA. The remaining 10% of the altered DMSA was in the form of cyclic disulfides of DMSA. So far, the mixed disulfide has been found in human but not in rabbit, mouse, or rat urine. Apparently there are species differences in how organisms metabolize meso-DMSA. Animal studies using meso-DMSA as an antidote for intoxication with aluminum, **arsenic**, bisbuth, cadmium, cobalt, copper, gold, mercury, platinum, manganese, polondium-210, an vanadium are summarized as are other properties of this dithiol chelating agent. The question still remains whether meso-DMSA is a **prodrug**.

=>